REMARKS

Upon entry of this amendment, claims 38 and 44-46 will be pending in the application. Claims 38, 44, 45 and 46 are amended herein.

Applicants renew their statement that a terminal disclaimer over U.S. Serial No. 09/921,157 will be submitted upon receipt of an indication of allowability.

35 U.S.C. §112, second paragraph

The Office Action maintains the rejection under 35 U.S.C. §112, second paragraph as being indefinite due to the inclusion of the word "substantially" and the phrases "substantially no toxicity" and "substantially reduced toxicity." While not conceding the correctness of the Office Action, Applicants herein amend claims 40, 63, 74 and 84 to remove the word "substantially." Therefore, the rejection that the degree of toxicity is unclear is obviated.

With respect to "toxicity" encompassing all forms of toxicity, including, for example, "cytotoxicity, endotoxicity, exotoxicity, cell-vacuolizing toxicity," Applicants invite the Examiner's attention to the Specification at page 5, lines 35-39, wherein it is described that the protein has "cytoxic [*sic*] activity." (Note that the typographical error is corrected herein). Furthermore, the cytotoxin causes vacuolization and death of a number of cell types. Thus, for clarity, the Applicants herein amend the claims to recite "no cytotoxic activity or reduced cytotoxic activity." This is specifically defined under the definition of cytotoxin, and would be easily understood by one of skill in the art reading the Applicants' specification.

Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §112, second paragraph.

35 U.S.C. §112, first paragraph (Enablement)

The Office Action rejects claims 38 and 44-46 under 35 U.S.C. §112, first paragraph, as allegedly failing to provide a sufficient disclosure to enable one of skill in the art to make and use the invention commensurate with the scope of the claims. Applicants respectfully disagree.

The Applicants teach at page 14, lines 21-30 that the polypeptides of the invention consist of at least 3-5 amino acids, and more preferably at least 8-10 amino acids, and even more preferably at least 11-15, or which is immunologically identifiable with a polypeptide encoded in the [designated] sequence." The specification also teaches that the antibodies raised against a portion of SEQ ID NO:3, including a 23 amino acid region of SEQ ID NO:3, recognize a 100 kDa protein that co-purifies with vacuolating activity from cytotoxin positive, but not cytotoxin negative strains of *Helicobacter pylori* (Specification at page 47, lines 10-30). The claims as originally filed, specifically state that the recombinant protein (which includes a derivative or fragment thereof with reference to claims 1 and 2) "exhibits substantially no toxicity, or substantially reduced toxicity."

The Office Action apparently misses the point of the citation to the paragraph bridging pages 5 and 6. This portion of the specification defines cytotoxin as having cytotoxic activity wherein the cytotoxin caused vacuolization and cell death. It is not meant to be a definition for what is exhibiting substantially no cytotoxicity or substantially reduced cytotoxicity. However, Applicants assert that it would be clear to one of skill in the art, when given a definition of cytotoxin, what would be lacking in cytotoxicity without a separate definition. A suggestion to the contrary defies reason.

Similarly, the Office Action suggests that the specification at pages 45 and 46 does not support the assertion that the antisera raised against a portion of the polypeptide having the amino acid sequence of SEQ ID NO:3 recognizes the native cytotoxin. The Office Action suggests that the identity of the amino acid sequence recognized in the native form (which is expected to be fully cytotoxic, is SEQ ID NO:3. Again, the Office Action misses the point. First, the cytotoxin is produced from cytotoxin positive strains of *H. pylori*, and is expected to be fully cytotoxic. That is completely beside the point. The antisera raised recognizes a protein in cytotoxin positive *but not cytotoxin negative* strains of *H. pylori*. Moreover, the apparent molecular weight of the protein recognized coincides with that known for the

cytotoxin. This provides *strong scientific evidence* that the antisera in fact recognizes the native cytotoxin, which is only present in cytotoxin positive strains of *H. pylori*. It must be remembered that it is the immunogenic fragments that have reduced or no toxicity, not the native protein. The experiment with the rabbit antisera demonstrates the principle claimed. Therefore, the Applicants have enabled the claims through demonstration of this working example.

The previous Office Action (mailed June 4, 2003) argues on page 7:

> [T]he specification teaches polypeptide molecules having amino acid substitutions 'that do not substantially affect the functional aspects', *i.e.*, cytotoxin polypeptides having amino acid substitutions such that their cytotoxic activity remains substantially the same as the native polypeptide. Therefore, using the Application as a guide, one of ordinary skill in the art would have been able to produce the cytotoxin polypeptides that retain cytotoxicity.

If this is so, then those polypeptides that did *not* retain their cytotoxic activity would be molecules identified as having substantially reduced or no cytotoxicity. Thus, if the guidance in the specification enables one of ordinary skill in the art to know when a polypeptide has been modified that retains cytotoxicity, by extension of reason, it also enables one of ordinary skill in the art to know when a polypeptide has been modified that loses cytotoxicity. Thus, the Office Action's argument against enablement actually supports enablement. It must be remembered that a great deal of experimentation is permitted, so long as it is not undue. When the Applicant provides guidance in the specification such that the experimentation necessary is routine, then undue experimentation is not required. The Office Action essentially concedes that the specification enables the modification of cytotoxins that retain cytotoxicity. Thus, it would be illogical to assert that it has not enabled modification of cytotoxins that do not retain cytotoxicity.

The Examiner concedes at page 8 of the Office Action: "It should be noted that the only place where the phrase 'substantially no toxicity' or 'substantially reduced toxicity' was mentioned in the specification as originally filed was in some original claims". Applicants note that the claims as filed form part of the disclosure and according to the MPEP:

> The claims as filed in the original specification are part of the disclosure and, therefore, if an application as originally filed contains a claim disclosing material not found in the remainder of the specification, the applicant may amend the specification to include the

> claimed subject matter. *In re Benno*, 768 F.2d 1340, 226 USPQ 683 (Fed. Cir. 1985). Thus, the written description requirement prevents an applicant from claiming subject matter that was not adequately described in the specification as filed.
>
> MPEP 2163.06 III at p. 2100-183.

The Applicants have also previously amended the Specification to include the language "substantially no toxicity" and "substantially reduced toxicity." Thus, support for the phrase is not lacking, as suggested by the Office Action. The filing of a patent application is a constructive reduction to practice, thus, as this aspect of the invention was present in the application *as filed*, it too was reduced to practice, not merely conceived, as suggested by the Office Action.

With regard to the description not providing guidance as to producing genetically detoxified toxins, the Office Action states that the genetic detoxification was not contemplated in the originally filed specification and rejects the statements of the Del Giudice Declaration as addressing pertussis toxin while not addressing the "unpredictability" factor. Applicants believe that the Office Action misses the point of the Declaration.

The Del Giudice Declaration refers to genetic detoxification of toxins as an art-recognized technique at the time of filing. The law makes clear that "not everything necessary to practice the invention needs to be disclosed. In fact, what is well-known is best omitted." *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991); MPEP § 2164.08. One of skill in the art, when faced with making the immunogenic portions of the SEQ ID NO:3 cytotoxin having substantially no, or reduced toxicity would look to the art to achieve this goal, and would rely on such techniques as disclosed in Pizza *et al.* (1989) "Mutants of pertussis toxin suitable for vaccine development" *Science* 246:497-500 (Del Giudice Declaration, paragraph 9). The Specification provides guidance to use techniques to modify the polypeptides of the invention at page 8, lines 13-23 wherein it is taught that in using recombinant polynucleotides, mutagenesis may be used to produce one or more altered polypeptides.

The Examiner concedes that one may be able to produce fragments of SEQ ID NO:3 and test their cytotoxicity and immunological identifiability. The Examiner, however, believes that "given the art-disclosed conformational complexity and functional unpredictability, the maintenance of immunological identifiability by an antibody specifically reactive with the native cytotoxin polypeptide of SEQ ID NO:3 along with the concurrent

recited attenuation in cytotoxic activity following one or more amino acid substitutions in the cytotoxin polypeptide, would not have been predictable." (Office Action of February 25, 2004, p. 9, lines 3133 through p. 10, lines 1-3).

The Office Action characterizes the Manetti reference as teaching the conformational complexity of a *Helicobacter pylori* cytotoxin polypeptide, and "[e]ven partial destruction of the conformational epitopes by chemical inactivation can result in lowering of the effective immunogenicity." However, the complexity of the conformation of the protein also likely affects toxicity. That is, the destruction of the conformational structure, such as by making fragments of SEQ ID NO:3, would likely produce polypeptides of reduced or no toxicity. Further, the claims require only that the polypeptides be immunogenic and recognize the native protein and exhibit reduced or no toxicity themselves. One of skill in the art, as conceded by the Examiner, may be able to test for immunological identifiabililty. Further, in the above quoted passage, Manetti referred to destruction of epitopes by chemical inactivation, not genetic detoxification. With respect to genetic detoxification, Manetti recognized the value of detoxified *H. pylori* cytotoxin *after* the Applicants in the instant application.

The Office Action emphasizes that unpredictability is "one of the *Wands* factors for enablement." However, Applicants note that the *Wands* factors must be considered as a whole and any one factor is not controlling. Moreover, the Office Action argues that dramatic differences may be seen in proteins in which a single amino acid is changed. However, the argument proves that even single amino acid differences can lead to substantially reduced toxicity or no toxicity, and the Applicants provide an example of immunizing with a portion of the cytotoxin which produces antisera that recognizes native structure. Thus, one of skill in the art could easily modify the cytotoxin of the invention, and determine whether the resulting cytotoxin was cytotoxic and immunogenic using the guidance of the specification and the knowledge in the art.

The Applicants provide a working example of the claimed invention and sufficient guidance to make and use the invention commensurate with the scope of the claims without undue experimentation. Accordingly, Applicants request reconsideration and withdrawal of the enablement rejection under 35 U.S.C. § 112, first paragraph.

35 U.S.C. §112, first paragraph (New Matter)

The Office Action maintains the rejection of claims 38 and 44-46 under 35 U.S.C. §112, first paragraph as allegedly containing new matter. Applicants respectfully disagree.

The Applicants disclose polypeptides of SEQ ID NO:3, that, when used as immunogens, elicit antibodies in animals that also recognize the native cytotoxic protein of *Helicobacter pylori*. The Examiner states in the Office Action "A non-recombinant polypeptide present in the protein extracts of a cytotoxin-producing strain of *H. pylori* is expected to be fully cytotoxic, as opposed to be substantially non-cytotoxic." (Office Action dated February 25, 2004, page 6, lines 13-14). However, the Applicants are not claiming that the native protein is non-cytotoxic, as the statement suggests, but that the *polypeptides of the invention* (useful as immunogens) are non-cytotoxic or have reduced cytotoxicity. The claim language includes the feature that the polypeptides of the invention are immunologically identifiable by antibodies that react specifically with the polypeptide having the amino acid sequence of SEQ ID NO:3 (*i.e.*, the same antibodies recognize the polypeptides as recognize the native protein having the amino acid of SEQ ID NO:3) and that the polypeptides exhibit no toxicity or reduced toxicity.

Moreover, the specification teaches at page 14, lines 21-30 that the polypeptides of the invention consist of at least 3-5 amino acids, and more preferably at least 8-10 amino acids, and even more preferably at least 11-15, or which is immunologically identifiable with a polypeptide encoded in the [designated] sequence." Thus, there is direct support for the phrase within the claims. The originally filed claims and the specification (amended to include the language of the originally filed claims) specify that the polypeptides of the invention exhibit substantially no toxicity or substantially reduced toxicity (see original claim 8, as filed and the amended specification at page 4 lines 1-4). Thus, no new matter is added.

Prompt withdrawal of the rejection is respectfully requested.

35 U.S.C. §102

The Office Action maintains the rejection of claims 38, and 44-46 under 35 U.S.C. §102 (e) as anticipated by U.S. Patent No. 6,054,132 to Cover *et al.* ("COVER I") under 35 U.S.C. §102 (b) as anticipated by Cover *et al.* (1992) *J. Biol. Chem.* 267:10570-10575 ("COVER II").

COVER I discloses the purification of a cytotoxin of *Helicobacter pylori* with vacuolating activity. COVER I specifically states at Col. 2, lines 7-9 "It is an object of the present invention to provide a substantially pure antigenic composition *with vacuolating toxin activity*" (emphasis added). Further the patent states that one embodiment of the invention is "a purified antigenic composition *with vacuolating toxin activity* (hereinafter termed CB antigen)" and the term CB antigen is defined as the "functionally active non-denatured vacuolating toxin" (col. 2, lines 37-39). Thus, COVER I does not teach or suggest the use of portions of the cytotoxin that exhibit substantially no, or substantially reduced cytotoxicity as claimed in the instant application.

The Office Action appears to believe that the Patent teaches a 23 amino acid fragment of the CB toxin which comprises the antigenic polypeptide. This is incorrect. The Patentees performed N-terminal sequencing on a purified toxin to deduce the amino acid composition and sequence of the N-terminus of the toxin. This portion was not used as an immunogen, rather, it was performed to partially characterize the entire CB toxin. The Examiner concludes:

> [t]hat the structurally identical 23 amino acid-long antigenic polypeptide of the prior art obtained from a purified toxin, is pure enough to be of substantially no endotoxicity, or of

> substantially reduced LPS-related toxicity and is long enough to be immunologically identifiable by antibodies specific to the amino acid sequence of SEQ ID NO:3 are inherent from the teachings of [COVER I]

However, as described above, this is simply factually incorrect, and therefore unfounded. COVER I did not obtain and purify a 23 amino acid fragment from the toxin. Such is neither the purpose nor the result of N-terminal sequencing.

Thus, COVER I does not teach every element of the claims and does not anticipate the claims within the meaning of 35 U.S.C. §102.

Likewise, COVER II teaches the purification to homogeneity of a vacuolating cytotoxin from *H. pylori*. One step in evaluating the purified protein in COVER II was to perform N-terminal amino acid sequencing to determine the amino acid sequence of the first 23 amino acids. Notably, COVER II did *not* purify a fragment of the cytotoxin comprising 23 amino acids. Amino acid sequencing breaks the peptide bond of the N-terminal amino acid and analyzes it, and subsequently the next amino acid is cleaved from the peptide chain. Thus, COVER II does not include every limitation of the claims and does not anticipate the claims within the meaning of 35 U.S.C. §102.

Withdrawal of the rejections under 35 U.S.C. §102 is respectfully requested.

The Office Action separately rejects claims 38 and 45 under 35 U.S.C. §102(e) as anticipated by COVER I).

As noted above in the discussion for the rejections over COVER I and COVER II, COVER I does not teach a fragment from a purified toxin that is long enough to be immunologically identifiable. No 23 amino acid fragment was purified in COVER I. Rather the amino acid sequenced was analyzed by identifying N-terminal amino acid sequence, cleaving one amino acid off at a time. No intact fragment of 23 amino acids was purified that

could be "immunologically identifiable, or which could be demonstrated to have substantially no endotoxicity or to exhibit substantially reduced endotoxicity, as suggested by the Office Action.

The Office Action further separately rejects claims 38 and 45 under 35 U.S.C. §102(b) over COVER II. As noted above, COVER II teaches the purification to homogeneity of a vacuolating cytotoxin from *H. pylori*. One step in evaluating the purified protein in COVER II was to perform N-terminal amino acid sequencing to determine the amino acid sequence of the first 23 amino acids. Notably, COVER II did *not* purify a fragment of the cytotoxin comprising 23 amino acids. Amino acid sequencing breaks the peptide bond of the N-terminal amino acid and analyzes it, and subsequently the next amino acid is cleaved from the peptide chain. Thus, COVER II does not include every limitation of the claims and does not anticipate the claims within the meaning of 35 U.S.C. §102.

Conclusion

Applicants respectfully request reconsideration in view of the foregoing amendments and remarks and urge prompt allowance of the claims.

If the Examiner believes a telephone conference would expedite prosecution of this application, the undersigned may be contacted at 215-564-8930.

Respectfully submitted,

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